REMARKS

The amendments to the specification expressly note the SEQ ID numbers of the sequences for brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), neurotrophin 4 (NT-4), and neurotrophin 4/5 (NT-4/5).

The amendments to the Sequence Listing include amino acid sequences for BDNF, NT-3, NT-4, and NT-4/5. Support for these amendments may be found, for example, in the application as originally filed at page 2, lines 8-11 (BDNF); page 2, lines 24-30 (BDNF, NT-3); page 2, lines 31-33 to page 3, lines 1-5 (NT-4 and NT-4/5). These and other references were explicitly incorporated by reference into the present application on page 117, lines 4-6. The amendments to the sequence listing also correct matters objected to by the USPTO in the Advisory Action mailed June 27, 2007.

The amendments to claim 6 find support in the application as filed, for example, at page 2, lines 8-19 an 31-32; page 3, lines 1-5; page 4, lines 9-10; page 10, lines 20-25; page 11, lines 3-11 as amended in the Amendment filed December 1, 2006; page 20, lines 30-33 to page 21, lines 1-10; page 41, lines 15-16 (trkB binds BDNF and NT-4/5); page 87, lines 14-17; Example 3, pages 109-112; page 112, lines 9-18; and elsewhere in the application as originally filed.

No new matter is added by way of the amendments to the specification, sequence listing, or the claims.

Priority

Applicants note the USPTO's acknowledgement that the priority of claims 6-9 and 12 of the present application is March 18, 1994, the filing date of the parent application U.S. Patent Application 08/215,139.

The Rejections of Claims 6-9 and 12 under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 6-9 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking clarity in the written description of "a neurotrophic factor", "human trkB receptor polypeptide", and NT-4 or NT-4/5." The USPTO suggests that *Falkner v. Inglis* does not apply in the instant application allegedly "because the claimed neurotrophic factor, human trkB receptor, or NT-4 or NT-4/5 encompass a genus of numerous variant neurotrophic factor and

human trkB receptor, or NT-4 or NT-4/5, the structure of which genus of variants is **not disclosed** in the specification, nor **in the art**, and cannot be predicted" (page 3, lines 18-22 of the Office Action dated March 8, 2007).

However, Applicants note that the present application discloses the structure, in the form of the amino acid sequences, of full-length human trkB receptor (SEQ ID NO: 2) and truncated human trkB receptor (SEQ ID NO: 4), and that the structures of NT-4 and NT-4/5 (e.g., amino acid sequences), as well as of BDNF and NT-3, were known at the time of the application, and were disclosed in the application in the cited references which were incorporated by reference in the original application. For example, the specification clearly discloses that the scientific literature provided substantial description, including sequences, of the neurotrophins NT-4 and NT-4/5 (see, e.g., page 2, lines 31-33 to page 3, lines 1-5, and elsewhere in the specification). Thus, one of ordinary skill in the art would know how to identify and how to use the neurotrophins NT-4 and NT-4/5 as required in the claims. As acknowledged by the USPTO, sequences of human trkB receptor and a splice variant of a human trkB receptor are disclosed in the application. Thus, it is clear that Applicants had possession of the claimed invention, including possession of the claimed "neurotrophic factor, human trkB receptor, or NT-4 or NT-4/5" at the time the invention was made.

Applicants note that the specification stands amended to include the amino acid sequences of NT-4 and NT-4/5 as required by the USPTO, from references which were cited and incorporated by reference in the application as originally filed (e.g., U.S. Application 07/587,707 (now U.S. Patent 5,364,769); Holbrook et al.; Berkemeier et al.; and Ip et al., as noted on pages 2-3 of the application as filed). Thus, the application includes all the materials said by the USPTO to be essential materials (pages 8-9 of the instant Office Action). In addition, the amino acid sequences of BDNF and NT-3 are also included in the amended Sequence Listing. These sequences were incorporated by reference in the application as originally filed (e.g., page 2, lines 9-11 and lines 24-30). Applicants note that the sequences of BDNF and NT-3 were disclosed in the application U.S. 07/494,024 (which has a related application, via continuation applications, which issued as U.S. Patent 6,174,701) which was incorporated by reference in the present application as originally filed.

Moreover, the claims, as amended, recite that the human trkB receptor of the claimed methods is a human trkB receptor polypeptide of SEQ ID NO:2 or SEQ ID NO:4, or an immunoadhesin thereof. Pursuant to the Restriction Requirement, the neurotrophins of the claimed methods are selected from NT-4, and NT-4/5, which are of known structure, and are not a "genus of variants" that is not disclosed in the application as alleged by the USPTO.

Accordingly, the claims being directed to specific human trkB receptors of known and disclosed sequence, and the claims being directed to the detection of specific neurotrophins of known and disclosed sequence, Applicants believe that the rejections to claims 6-9 and 12 under 35 U.S. C. § 112, first paragraph for alleged lack of clear written description are overcome.

A. Enablement

The Rejections of Claims 6-9 and 12 under 35 U.S.C. § 112, First Paragraph, Enablement

The Wands Factors

Claims 6-9, and 12 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly failing to comply with the enablement requirement, the USPTO suggesting that the pending claims lack "enablement for a method of diagnosis of any pathological condition, any malignancy, any tumor or any pancreatic disorder that over-or underexpresses a neurotrophic factor, or NT-4 or NT-5" (page 4, lines 15-17 of the Office Action mailed March 8, 2007).

Applicants note that the neurotrophic factor of the present claims is selected from the group consisting of BDNF (SEQ ID NO: 42), NT-3 (SEQ ID NO:43), NT-4 (SEQ ID NO: 44) and NT-4/5 (SEQ ID NO: 45) and is capable of binding a human trkB receptor polypeptide of SEQ ID NO:2 or SEQ ID NO:4 or an immunoadhesin thereof. (Applicants note that the claims include the (withdrawn) neurotrophins BDNF and NT-3 since, per page 2, lines 12-14 of the Office Action mailed October 24, 2006, upon allowance of claim 6 with regard to NT-4 and NT-4/5, the claims may be examined with respect to BDNF and NT-3 as well). Thus, the USPTO's recitation of the requirements of the claims is in error where it suggests that NT-4 or NT-4/5 are somehow different than "a neurotrophic factor" when, in fact, they are each individual members of the group of neurotrophic factors which may satisfy the requirements of the claimed invention.

Applicants submit that an analysis of the present claims in view of the factors enumerated in *In re Wands* (8 USPQ2d 1400 (Fed. Cir. 1988)) results in the conclusion that the present claims are enabled by the disclosure of the specification as filed and in view of the skill and knowledge of one of ordinary skill in the art.

Applying the *In re Wands* factors to the present claims, we find that:

1) The nature of the invention:

The claims are drawn to methods for diagnosis of pathological conditions. The USPTO suggests that the claimed method is "not routine" and suggests that "there is no correlation between the claimed over- or underexpression of a neurotrophic factor, or NT-4 or NT-4/5 and a pathological condition" (page 5, lines 8-10). However, the claimed methods all require the same routine steps of contacting a sample and of detecting the presence of the neurotrophic factor, are methods comprised of routine laboratory or clinical operations, and are not complex since they all share the same, few steps, and thus the nature of the invention is not complex.

Moreover, the specification clearly discloses that these named pathological conditions may be diagnosed by the detection of over- or underexpression of a neurotrophin by detecting binding to a trk receptor (page 10, lines 20-25), such as a human trkB polypeptide (page 6, lines 7-32), and that the neurotrophin may be selected from BDNF, NT-3, NT-4, and NT-4/5 (page 16, lines 1-2).

2) The state of the prior art:

As acknowledged by the USPTO, the closest prior art fails to teach detection of NT-4 using human trkB receptor (page 5, lines 18-20 of the Office Action mailed March 8, 2007), as required by the claimed invention. Applicants note that the cited reference, termed "the closest prior art," demonstrates that one can detect a malignancy, such as pancreatic cancer, by detecting the underexpression of NT-4. Thus, the state of the prior art is supportive of enablement of the present invention.

3) The relative skill of those in the art:

Applicants reiterate that the relative skill of those in the art is high. The USPTO suggests that the skill level may not be high, apparently because the USPTO suggests that "one cannot

predict that the claimed neurotrophic factor is over- or underexpressed in a pathological condition" (page 6, lines 7-9 of the Office Action mailed March 8, 2007). However, Applicants do not believe that undue experimentation would be required to practice the invention since detection of labeled polypeptides is well-known and routine in the art, since the specification provides detailed explanation and examples related to the claimed methods (see, e.g., pages 79-81; 86-90, particularly 86-87; and elsewhere in the application), and since it would be a matter of routine to measure over- or underexpression of a neurotropic factor selected from the group consisting of NT-4 and NT-4/5 by measuring their binding to labeled human trkB receptor polypeptide.

4) The predictability or unpredictability of the art:

The USPTO suggests that "which pathological conditions, which malignancy, which tumor or which pancreatic disease under- or over-expresses the claimed neurotrophic factor, or NT-4 or NT-4/5 is not predictable" and cites certain scientific articles to suggest that trkA, trkB, and trkC may be expressed differently in different diseases (pages 6-7, Office action mailed March 8, 2007). However, diagnostic methods are known in the art and are predictable; the application discloses the particular and novel aspects of the claimed methods, which are also predictable in that they rely on the disclosed sequences and are also based on methods and skills that are well-known in the art. Moreover, Applicants submit that the predictability of biotechnological arts is high where (as here) specific sequences are known in the art, in that methods for producing proteins and nucleic acids of known sequence are well-known and predictable, and that methods for producing desired variants of such sequences are also well-known and predictable. In addition, the application as filed explicitly discloses the pathological conditions to which the claimed diagnostic methods are directed; thus, Applicants submit that the predictability of the art related to such diagnostic methods is quite high.

The USPTO cites Soontorniniyooomkij et al. and Guate et al. as suggesting that the level of expression of a protein in a disease is unpredictable. Applicants note that these references, directed to measurements of levels of neurotrophins and/or neurotrophin receptors, demonstrate that one of ordinary skill in the art would be able to practice and use the claimed methods, since these references discuss neurotrophin levels, using different methods, but showing that such

measurements were possible and known to be of scientific and diagnostic value at the time of the invention.

The USPTO also suggests that "one cannot predict that NT-4 or NT-4/5 is the only ligand for the trkB receptor" (page 7, lines 13-14). Applicants do note that the specification provides data for BDNF and NT-3 binding to trkB; thus, BDNF and NT-3 may bind to the trkB receptor. However, even if other ligands, in addition to NT-4 or NT-4/5 may bind the human trkB receptor polypeptide comprising SEQ ID NO:2 or SEQ ID NO:4, or an immunoadhesin thereof, such binding may be diagnostic of a pathological condition. In addition, although presently only NT-4 and NT-4/5 are under examination pursuant to the Restriction Requirement, upon allowance of the linking claim 6, the restriction requirement as to the linked inventions will be withdrawn (page 2, lines 12-14). Thus, upon allowance of the linking claim, Applicants believe that the objection as to possible BDNF or NT-3 binding to trkB receptor polypeptides will be moot.

5) The breadth of the claims:

The USPTO suggests that the claims are broad (page 7, lines 15-22 of the Office Action mailed March 8, 2007), noting that they encompass numerous possible pathological conditions. However, merely encompassing numerous conditions is not believed to be grounds for objection where the specification and claims describe the methods and provide the means for diagnosing such numerous conditions. Applicants note that all claims require that the pathological condition to be diagnosed be one that is "characterized by the over- or underexpression of a neurotrophic factor" and is thus limited to those conditions having that identified characteristic. The fact that such conditions may include the named particular manifestations, such as a malignancy (claim 7), or a tumor (claim 8), or a pancreatic disorder (claim 9), does not increase the breadth of the claim, as all the claims are limited to methods related to disorders with the named characteristic (over- or underexpression of a neurotrophic factor). Thus, the claims are not broad in that the claimed subject matter is explicitly recited in the claims and limited to particular pathological conditions all exhibiting the named identifying characteristic.

6) The amount of direction or guidance provided, and

7) The presence or absence of working examples:

The USPTO suggests that undue experimentation would be required to practice the claimed invention (page 8, lines 17-18 of the Office Action mailed March 8, 2007). However, the application teaches how to measure levels of neurotrophins of interest in tissue using the novel trkB polypeptides of the claims. In addition, the scientific literature demonstrates that neurotrophin measurements were possible by other means as well (see, for example, the references cited by the USPTO, including, for example, Soontorniniyooomkij et al.). Moreover, it is well known that one can measure levels of a molecule of interest in normal tissue as well as in diseased tissue, and thus compare levels of that molecule of interest in control and in test tissue samples. Thus, the application disclosing and teaching methods for measuring neurorophin levels in tissue, which can be normal or diseased tissue, Applicants submit that the application provides sufficient guidance and direction as to enable one of ordinary skill in the art to practice the invention without undue experimentation.

Accordingly, the analysis of the *In re Wands* factors indicating that the amount of experimentation required to practice the invention is not undue, Applicants submit that the claims are enabled and that the rejections of claims 6-9, and 12 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement are overcome.

B. Essential Materials

Claims 6-9, and 12 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly requiring essential materials NT-4 and NT-4/5 "which are however only incorporated by reference to publications in the art" and the USPTO has required that the application be amended to disclose the material incorporated by reference (page 16, lines 18-22, Office Action mailed October 24, 2006).

As amended, the application now includes the sequences of NT-4 (SEQ ID NO: 44) and NT-4/5 (SEQ ID NO: 45) (and also BDNF (SEQ ID NO: 42) and NT-3 (SEQ ID NO:43)).

Accordingly, since the sequences of these neurotrophic factors were incorporated by reference in the application as originally filed, and the application has now been amended to include that material that was incorporated by reference, Applicants believe that the rejections of

claims 6-9, and 12 under 35 U.S.C. § 112, first paragraph as allegedly failing to recite essential materials are overcome.

The Rejections of Claims 6-9, and 12 under 35 U.S.C. § 112, 2nd paragraph

Claims 6-9 and 12 stand rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly being indefinite, for allegedly not being clear "as to what" the "over- or underexpression of a neurotrophic factor" was compared to (page 9, lines 6-16). However, as amended, claim 1 recites that the diagnosis is made "if said neurotrophic factor is over- or underexpressed in said sample **as compared to expression of said neurotrophic factor measured in a sample from a normal subject**." Thus, the claim recites the comparison to be made, thus fulfilling the criterion suggested by the USPTO.

Applicants submit that the application as originally filed discloses comparison of levels of molecules of interest, such as neurotrophins, as found in normal and diseased tissues.

Applicants note that the application, as originally filed, discloses:

"A method for the diagnosis of a pathological condition characterized by the over- or underexpression of a neurotrophic factor, comprising contacting a biological sample comprising said neurotrophic factor with a detectably labelled trk receptor polypeptide capable of binding said neurotrophic factor, and detecting the marker so bound." (page 10, lines 20-25).

and

"With the information in hand about the forms of trk present in human, it is possible to begin to investigate the expression of these forms in the normal and diseased state. Knowledge of the expression levels of the entire spectrum of forms of each trk will be crucial, as the different forms can display different and sometimes counteracting signal transduction properties in response to neurotrophins. In addition, the availability of soluble forms of the human trks should, by allowing the blocking of endogenous bioactivity, accelerate the investigation of the biology of neurotrophins in vivo." (page 112, lines 9-18).

As disclosed in the application, including in the passages quoted immediately above, Applicants have disclosed their methods and stated that expression of molecules of interest

(explicitly as in "accelerate the investigation of the biology of neurotrophins in vivo," and implicitly in the "forms of trk present in the human" and in view of the discussion elsewhere in the application about neurotrophin levels) may be compared to normal levels, as stated on page 112, line 11.

Applicants further note that, at the time the application was filed, it was well known to measure levels of a molecule of interest in normal tissue as well as in diseased tissue, and thus compare levels of that molecule of interest in control and in test tissue samples. Thus, the application disclosing comparison of normal and diseased state in the application as originally filed, and teaching methods for measuring neurorophin levels in tissue, which can be normal or diseased tissue, and as claimed in amended claim 6, Applicants believe that the rejections of claims 6-9 and 12 under 35 U.S.C. § 112, 2nd paragraph are overcome.

CONCLUSION

Applicants respectfully request the entrance of the amendments and reconsideration and allowance of the claims 6-9 and 12. In view of the allowable subject matter of the linking claim, claim 6, Applicants further request that the restriction requirement be withdrawn and that the remaining claims and subject matter be examined and allowed. Early notification of the allowance of the application is respectfully requested.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Fees related to the Request for Continued Examination, and for an extension of time of two months is believed to be due. Please charge these fees, and for any other extension of time and for any other fees due, to Deposit Account No. **08-1641** (**Attorney's Docket No. 39766-0033 CP2C2C1**).

Respectfully Submitted,

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